DIAGNOSIS OF MARFAN SYNDROME

D / AMAT

History

- **Antoine Bernard-Jean Marfan** (June 23, 1858 – February 11, 1942), a French pediatrician.
- In 1896, Marfan described a hereditary disorder of connective tissue in a 5 yr old girl with disproportionately long limbs that later became to be known as Marfan syndrome

Epidemiology

- One of the most common inherited disorders of connective tissue
- Incidence: 1 in 3000-5000 individuals
- Prevalence is thought to be similar
  - Regardless of sex
  - Regardless of ethnicity

Marfan syndrome-diagnosis and management. *Curr Probl Cardiol*. Jan 2008;33(1):7-39.

Aetiology

- Caused by a variety of mutations in the FBN1 gene. FBN1 mutations have been identified in over 90 percent patients
  - In 75% of patients - autosomal dominant, although the appearance of family members and degree of pathological features may vary.
  - In 25% of patients - mutation occurs spontaneously and may be associated with older paternal age.
- The first fibrillin-1 gene mutation was identified in 1990. Subsequently, over 1000 different mutations have been identified.

- About 10 percent of individuals with suspected MFS have no defined FBN1 mutation. Some of these individuals may have TGFBR1 or TGFBR2 mutations. TGFBR1/TGFBR2 mutations more typically cause LoeysDietz syndrome (LDS), with rare reports in association with familial thoracic aortic aneurysm (FTAA) syndrome.
- Some patients with FBN1 gene mutations do not have MFS and instead have a related disorder such as ectopia lentis syndrome or other diseases such as ShprintzenGoldberg syndrome, WeillMarchesani syndrome, or stiff skin syndrome.

Pathophysiology

- Mutations in the fibrillin-1 gene result in the production of an abnormal fibrillin protein, leading to abnormalities in the mechanical stability and elastic properties of connective tissue.
- More recently, research suggests that transforming growth factor-beta is implicated in the failure of normal elastic tissue formation.
- TGFBR 1 and 2 mutations – may have similar manifestations
- Cystic medial necrosis - cysts being fluid collections of mucin and ground substance - lead to a weakening of the aortic wall with subsequent aortic dilation and potentially aortic dissection, aneurysms, and rupture. They also lead to a reduction of the structural integrity of the skin, ligaments, eye lenses, lung airways, and the spinal dura.

Diagnosis of Marfan Syndrome

Clinical Manifestations

Diagnostic Criteria

Step by step Approach

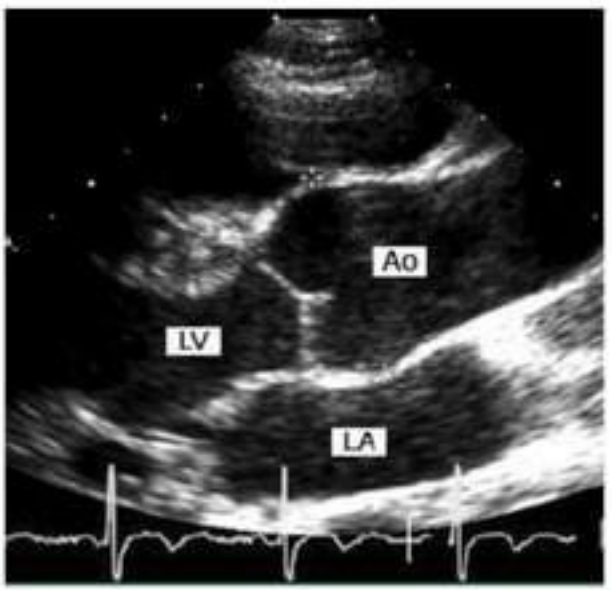
- First description
  - 5 year girl, Gabrielle P
  - Prominent Skeletal features - disproportionately long limbs.
  - She Probably had Congenital Contractual arachnodactyly! - Not Marfan!

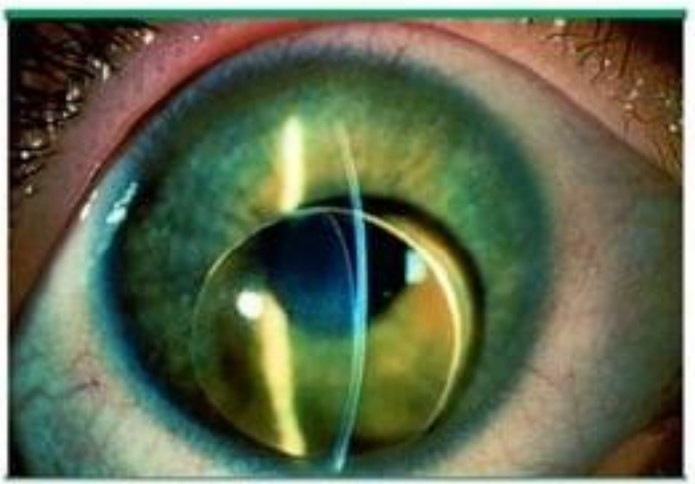
Revised diagnostic criteria for Marfan syndrome.
American Journal of Medical Genetics. 62 (1996)

- Additional features described during 20th century
  - Ectopia Lentis (Borger; 1914)
  - Autosomal Dominant inheritance (Weve; 1931)
  - Aortic Dialatation (Etter and grover; 1943)
  - Aortic Dissection (Baer; 1943)
  - Mitral Valve Prolapse (Brown; 1975)
  - Dural Ectasia (Pyeritz; 1988)

Revised diagnostic criteria for Marfan syndrome.
American Journal of Medical Genetics. 62 (1996)

- Highly variable phenotypic expression
- 2 cardinal features with various supportive features
  - Aortic root dialatation
  - Ectopia lentis





The Berlin Nosology

- 'Clinical' Classification of Heritable connective tissue disorders (HCTD)
- Described Marfan Syndrome
- Major and Minor manifestations (in decreasing order of specificity)
  - Skeletal
  - Ocular
  - Cardiovascular
  - Pulmonary
  - Skin
  - CNS
  - Autosomal Dominant Inheritance

International Nosology of HCTD,1986
American Journal of Medical Genetics. (1988)

- Relied completely on clinical criteria
- Led to overdiagnosis
  - Specially in family members of index cases
  - Overlapping HCTDs

International Nosology of HCTD,1986
American Journal of Medical Genetics. (1988)

The Ghent Criteria

- Introduced in 1996
- For more accurate identification and decreasing overdiagnosis – less weightage to less specific signs and symptoms
- Major criteria – High specificity (less likely in overlapping disorders)
- Differentiates between
  - Major criteria present in a system
  - A system 'being involved' – minor criterion
- If a number of minor criteria present – conversion to major criteria

Revised diagnostic criteria for Marfan syndrome.
American Journal of Medical Genetics. 62 (1996)

Table 1. Ghent diagnostic nosology

System	Major criterion	Involvement
Cardiovascular	Dilatation of the aortic root	Mitral valve prolapse
	Dissection of the ascending aorta	Dilatation of the pulmonary artery, below age 40
		Calcified mitral annulus, below age 40
		Other dilatation or dissection of the aorta
Skeletal	At least 4 of the following features:	2 of the major features, or 1 major feature and 2 of the following:
	Pectus carinatum	Pectus excavatum
	Pectus excavatum requiring surgery	Joint hypermobility
	Upper: lower segment ratio <0.86 or span: height >1.05	High palate with dental
	Wrist and thumb signs	Crowding
	Scoliosis >20° or spondylolisthesis	Characteristic face
	Reduced elbow extension (<170°)	
	Pes planus	
	Protrusio acetabulae	
Ocular	Lens dislocation (ectopia lentis)	Flat cornea
		Increased axial length of globe (causing myopia)
		Hypoplastic iris or ciliary muscle (causing decreased miosis)
Pulmonary	None	Spontaneous pneumothorax
		Apical blebs
Skin/Integument	None	Striae atrophicae
		Recurrent or incisional hernia
Dura	Lumbosacral dural ectasia	None
Genetic findings	Parent, child or sibling meets these criteria independently	None
	Fibrillin 1 mutation known to cause Marfan syndrome	
	Inheritance of DNA marker haplotype linked to Marfan syndrome in the family	

Requirement for diagnosis

Index Case

- If Characteristic Mutation known/AD inheritance apparent

  Major criteria in 1 system

  +

  2nd system 'involved'

- If family/genetic history not significant

  Major criteria in 2 systems

  +

  3rd system 'involved'

Relative of Index case

- Family history Major criteria present

  +

  Major criteria in 1 system

  +

  2nd system 'involved'

- Limitations
  - Insufficient validation
  - Limited applicability to children
  - Requirement of expensive and specialized evaluation
  - Overdiagnosis even when Aorta not involved – clinically less important phenotype
  - Dural ectasia, a major criteria, is often seen in other connective tissue disorders (including both LDS and SGS)

Revised Ghent Criteria

- Introduced in 2010
- Emphasis on the key features of Marfan syndrome
  - Aortic root aneurysm/ aortic root dissection
  - Ectopia lentis
- New systemic score assigns less specific features of Marfan syndrome a numeric value so they are weighted properly in the evaluation process.
- Highlights the identification of additional features that would suggest an alternative diagnosis
- Provides a more precise role for molecular testing

The revised Ghent nosology for the Marfan syndrome
J Med Genet 2010; 47:476.

- Criteria for Marfan syndrome diagnosis in patients with no family history
  - Ao ($Z \geq 2$) AND ectopia lentis
  - Ao ($Z \geq 2$) AND *FBN1* mutation
  - Ao ($Z \geq 2$) AND systemic features (≥ 7 points)
  - Ectopia lentis AND *FBN1* associated with known aortic involvement

Ao = aortic diameter above indicated Z-score or aortic root dissection

- Criteria for Marfan syndrome diagnosis in patients with a positive family history

  - Ectopia lentis AND family history of MFS
  - Systemic features (≥ 7 points) AND family history of MFS
  - Ao family history of MFS
    (Z ≥ 2 above 20 years, ≥ 3 below 20 years)

2 Scoring of systemic features for the diagnosis of Marfan syndrome*

Feature	Score
Wrist OR thumb sign†	1
Wrist AND thumb signs†	3
Pectus carinatum deformity	2
Hindfoot deformity	2
Plain pes planus	1
Pectus excavatum or chest asymmetry	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabulae	2
Reduced upper segment to lower segment ratio,‡ AND increased ratio of arm span to height§ AND no severe scoliosis	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Three of the five typical facial features (dolichocephaly, enophthalmos, downward slanting palpebral fissures, malar hypoplasia, retrognathia)	1
Skin striae	1
Myopia of >3 dioptres	1
Mitral valve prolapse	1

- Maximum Total = **20**
- **Systemic Involvement** if Total **≥ 7**

- Special considerations for children (<20 yrs):
  - If insufficient systemic features (<7) and/or borderline aortic root measurements (Z < 3) are present (without *FBN1* mutation) – "**non-specific connective tissue disorder**" until follow-up echo evaluation shows aortic root dilation (Z≥3).
  - If an *FBN1* mutation is identified in sporadic or familial cases but aortic root measurements are still Z < 3 - "**potential MFS**" until the aorta reaches threshold.

Related disorders

- **Ectopia lentis syndrome**
  - Dislocated lenses with or without systemic features AND
  - with an *FBN1* not associated with Ao
  - or no *FBN1*

- **MASS** (myopia, MVP, borderline aortic root dilation, striae, skeletal findings)
  - Ao ($Z < 2$); AND systemic features ≥ 5 (with at least one skeletal feature) without ectopia lentis

- **Mitral valve prolapse syndrome**
  - MVP; AND
  - Ao ($Z < 2$); AND systemic features < 5 without ectopia lentis

Aortic Disease

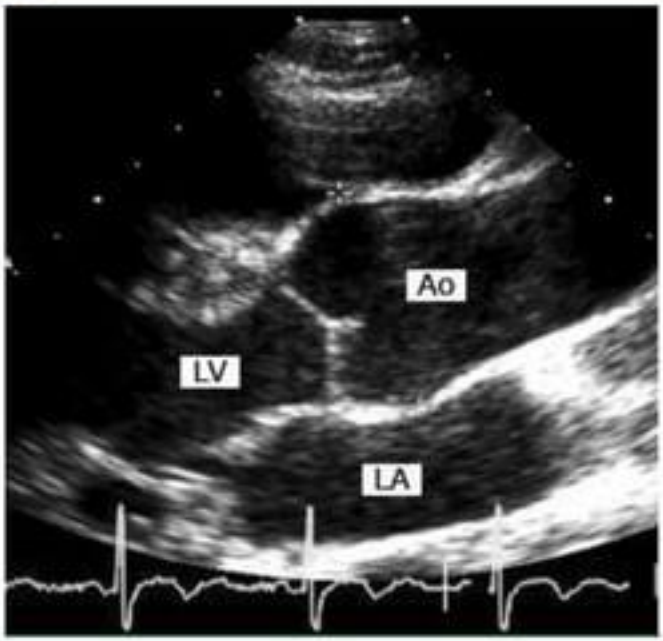
- Aortic root disease, leading to aneurysmal dilatation, aortic regurgitation, and dissection - main cause of morbidity and mortality
- Poor correlation between the severity of the cardiovascular and the ocular or skeletal manifestations
- Although dilated, the aorta in MFS tends to be stiffer and less distensible
- Dilatation of the aorta, often (about 25%) accompanied by aortic regurgitation, progresses with time
    - 50 percent of young children with MFS
    - 60 to 80 percent of adult patients with MFS

- Dilatation may also involve other segments of the thoracic aorta, the abdominal aorta, the root of the pulmonary artery or even the carotid and intracranial arteries, although much less frequent than in LDS.
- The normal range for aortic diameter varies with body size and age - nomograms and Z-scores used to identify aortic dilatation.
- Undiagnosed and untreated MFS - frequently associated with aortic dissection. May have a family history of dissection.
- The frequency with which MFS is responsible for aortic dissection varies with age.

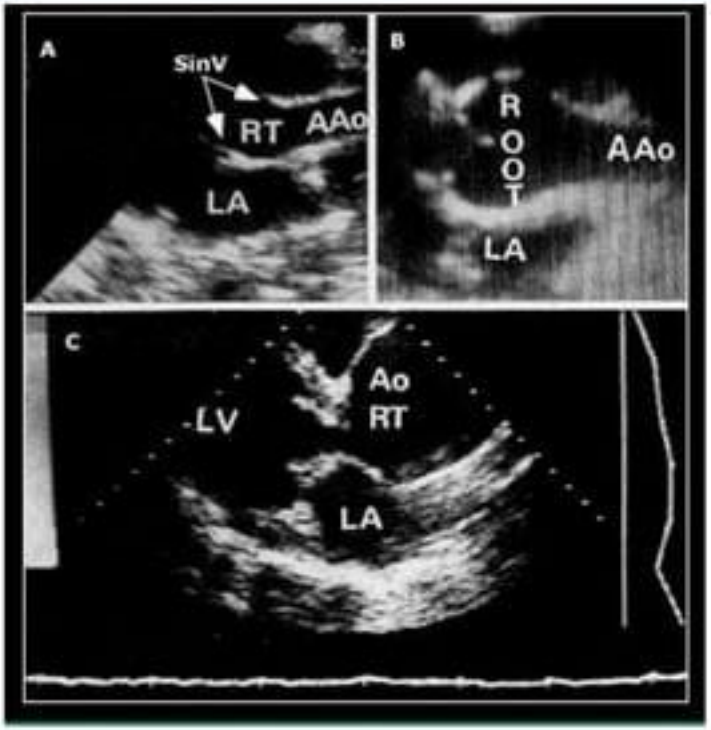
  50% of those under age 40

  2 % of those with age 40 - 70

  no patient over age 70



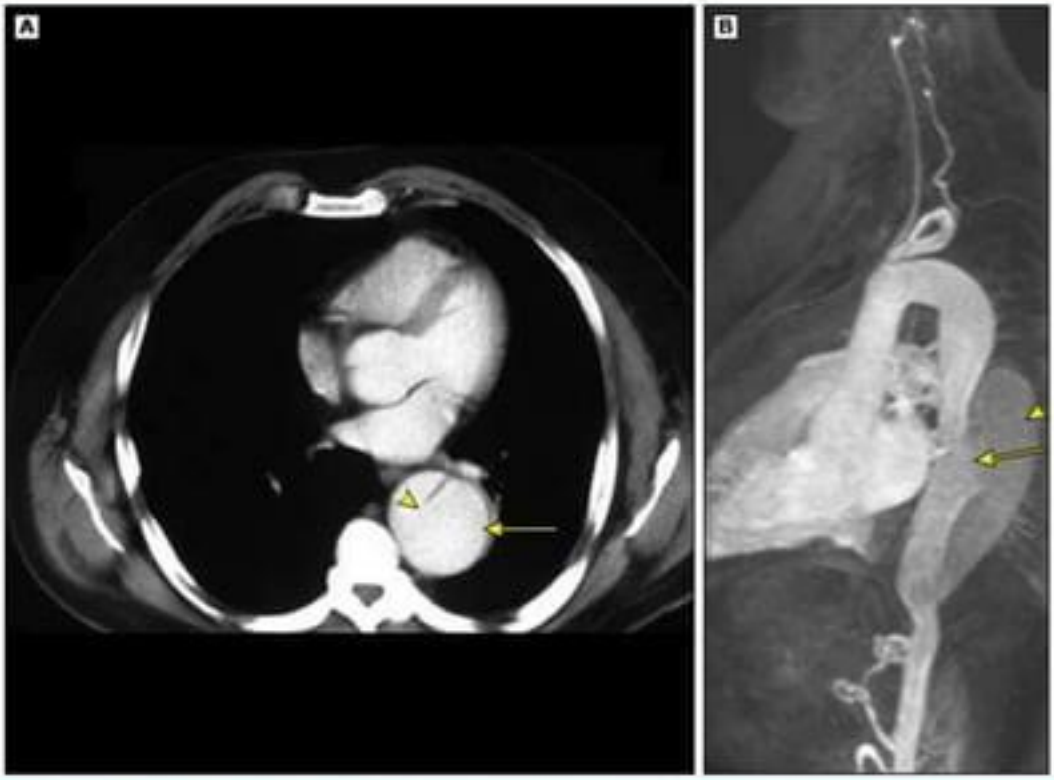
MFS; Ao root dialation



A	Normal
B	MFS; Ao root dialation
C	Aorto Annular ectasia; whole Asc Ao dialation

Chest radiograph in a patient with Marfan syndrome. Features include hyperinflation, bullous changes, dilated tortuous aorta, and "tall" lungs.

In this coronal CT view, the aortic root is dilated at the level of the sinuses of Valsalva.



A CT image through the heart (A) shows a communication (arrowhead) between the true lumen of the thoracic aorta and a large compressive false lumen (arrow). Image B is an MRI of the aorta in the lateral projection and shows a focal dissection with communication at mid aortic level (arrow) between the true lumen and the false lumen (arrowhead).

Cardiac disease

- Mitral valve prolapse (MVP)

  Common but nonspecific – only 1 point in systemic scoring

  40-54% MFS adults; upto 90% in some series

  frequency of MVP increases with age; greater in women.

  Tricuspid valve prolapse may also occur.

- On echo mitral leaflets elongated and redundant

  either or both leaflets may prolapse

  most have mild or less regurgitation

- Approximately 25 percent of patients with MVP have progressive disease - defined by the appearance or worsening of clinical symptoms of mitral regurgitation or worsening on echocardiography.
- Heart failure attributable to mitral valve prolapse and regurgitation represents a major source of morbidity and mortality in young children with the most extreme and rapidly progressive presentation of MFS.
- Some report suggest - some patients may have a cardiomyopathy with biventricular enlargement and generally asymptomatic mild systolic dysfunction unrelated to valvular disease

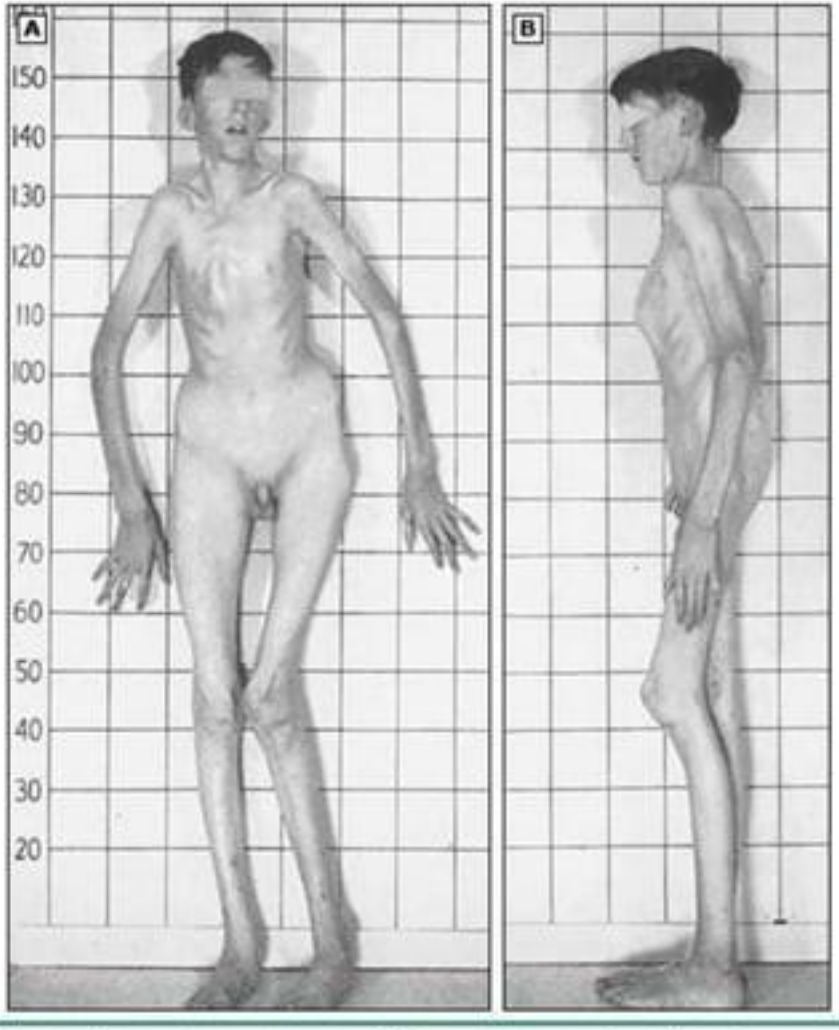
Skeletal disease

- Excess linear growth of the long bones – Individuals taller than predicted by their genetic background
- Joint laxity
- Paradoxically, some individuals with MFS have reduced joint mobility, particularly of the elbow and digits - reduced elbow extension (≤170 degrees with full extension) – 1 point to the systemic score
- **Arachnodactyly** — abnomally long and slender fingers
- **Thumb sign** - entire distal phalanx protrudes beyond the ulnar border of a clenched fist with or without the assistance of the patient or examiner to achieve maximum adduction

- **Wrist sign -** the top of the thumb covers the entire fingernail of the fifth finger when wrapped around the contralateral wrist
- **Pectus deformity** — Pectus carinatum - more specific for MFS than pectus excavatum or chest asymmetry,
- **Hindfoot valgus** — occurs with forefoot abduction and lowering of the midfoot and should be evaluated from anterior and posterior views.
- **Pes planus** (flat foot) without hindfoot valgus is less specific
- Generalized joint hypermobility also may occur, producing findings that overlap with the much more common benign **joint hypermobility syndrome**.

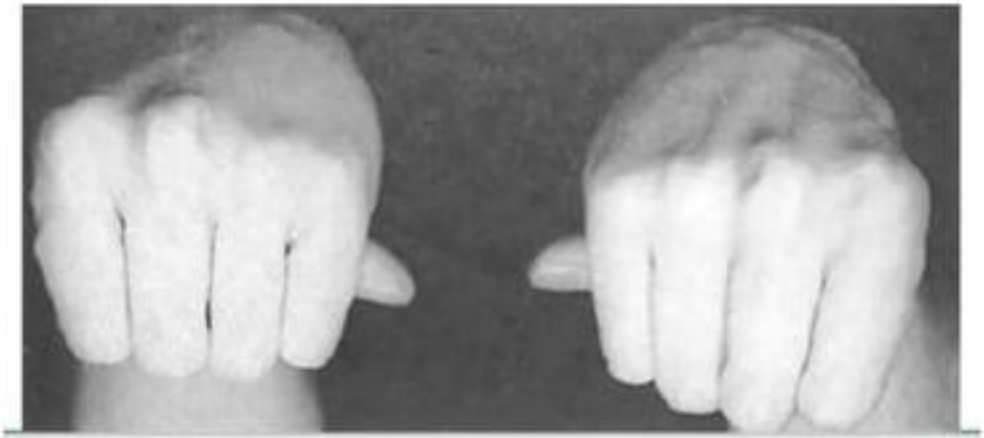
- **Abnormal US/LS and arm span/height** — disproportionately long extremities in comparison to the length of the trunk (dolichostenomelia) - upper segment to lower segment (US/LS) ratio is decreased and the arm span to height ratio is increased.
- The lower segment is defined as the distance from the top of the symphysis pubis to the floor in the standing position; The upper segment is the height minus the lower segment.

- Thresholds for abnormal US/LS and arm span/height vary with age and ethnicity.
- Reduced US/LS is <0.85 for white adults and <0.78 for black adults.
- For children, reduced US/LS is <1 for age 0 to 5 years, <0.95 for 6 to 7 years, <0.9 for 8 to 9 years, and <0.85 above age 10 years.
- Arm span measured by distance from tip of the middle finger on one hand to the other.
- Increased arm span to height ratio is >1.05 for adults.



Marfan syndrome in a 14-year-old boy. Note arachnodactyly, relatively long limbs (dolichostenomelia), pectus carinatum, sparse subcutaneous fat, unilateral genu valgum, and pes planus. Ectopia lentis and scoliosis also were present. This patient died of aortic rupture at age 15 years.

The wrist sign in a patient with Marfan syndrome. In a positive test, the first phalanges of the thumb and fifth digit substantially overlap when wrapped around the opposite wrist.



Steinberg thumb sign in a patient with Marfan syndrome. A positive test, such as this, consists of the distal phalanx of the thumb protruding beyond the ulnar border of the clenched fist and reflects both longitudinal laxity of the hand and a long thumb.

Thumb
Sign

- **Scoliosis and kyphosis**

  A Cobb's angle of at least 20 degrees (on an anterior-posterior radiographic view of the spine, the angle between a line drawn along the superior end plate of the superior end vertebra and a second line drawn along the inferior end plate of the inferior end vertebra of the scoliosis)

  Exaggerated kyphotic thoracolumbar spinal curvature.

- **Protrusio acetabuli**

  Can be diagnosed by plain radiograph, computed tomography (CT), or magnetic resonance imaging (MRI).

  On an anterior-posterior pelvic film, medial protrusion of the acetabulum ≥3 mm beyond the ilio-ischial (Kohler) line is diagnostic.

Protrusio acetabuli - medial displacement of the femoral head
Medial aspect of femoral cortex is medial to the ilioischial line.

- **Facial features** — dolichocephaly (reduced cephalic index or head width/length ratio), enophthalmos, downslanting palpebral fissures, malar hypoplasia, and retrognathia.

- **Dural ectasia**

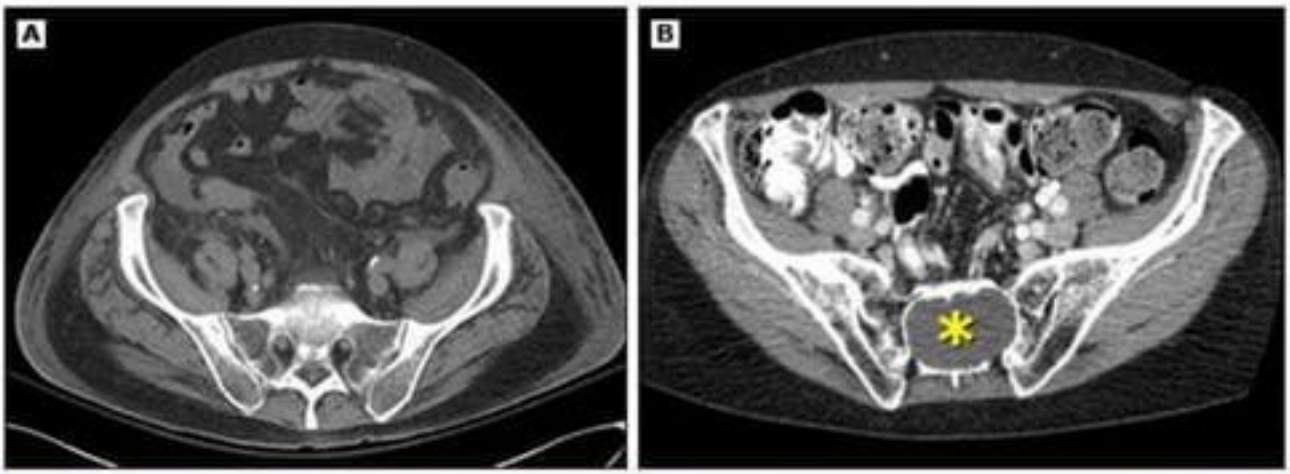
  Enlargement of the spinal canal owing to progressive ectasia of dura and neural foramina and to erosion of vertebral bone.

  Usually involves the lumbosacral spine

  60-90% pts on MRI/CT - sensitive but not specific sign of MFS, is commonly seen in Loeys-Dietz syndrome and Shprintzen-Goldberg syndrome, has been reported in the vascular form of Ehlers-Danlos syndrome.

  MRI most sensitive technique.

  No correlation appears to exist between the severity of dural ectasia and the degree of aortic dilatation.

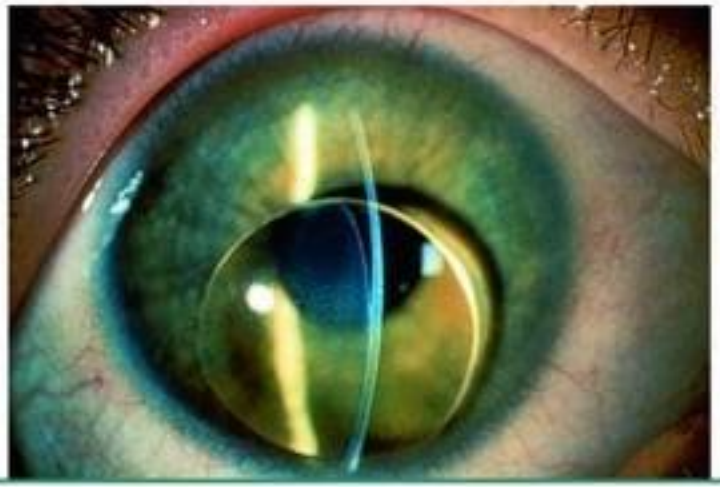


Computerized tomography of the pelvis demonstrates (A) normal spinal canal and (B) features of lumbosacral dural ectasia (asterisk). Note dilation of the spinal canal. This may be associated with pain and headaches.

Ocular abnormalities

- Ectopia lentis - 50 to 80 percent.

  Detected on slit-lamp examination after maximal dilatation of the pupil and the lens is usually displaced upward and temporally. It is caused by failure of the supporting ciliary zonules.
- Myopia >3 diopters - secondary myopia due to increased axis globe length.
- Flat cornea, hypoplastic iris, hypoplastic ciliary muscle causing decreased miosis, retinal detachment, glaucoma, and early cataract formation. Retinal tears and detachment are commonly bilateral.



Slit-lamp photomicrography shows ectopia lentis with microspherophakia; the lens is completely luxated into the anterior chamber, predisposing to pupillary block glaucoma.

- **Pulmonary disease** — Some patients develop emphysematous changes with lung bullae predominantly in the upper lobes, can predispose to spontaneous pneumothorax
- **Skin striae** — The presence of striae atrophicae contributes one point to the systemic score if not associated with pronounced weight changes or pregnancy and if in uncommon location such as the mid back, lumbar region, upper arm, axillary region, or thigh
- **Other** — Recurrent or incisional herniae, joint hypermobility, and high arched palate may occur but are **not** included in the systemic score - nonspecific.

Step-by-step diagnostic approach

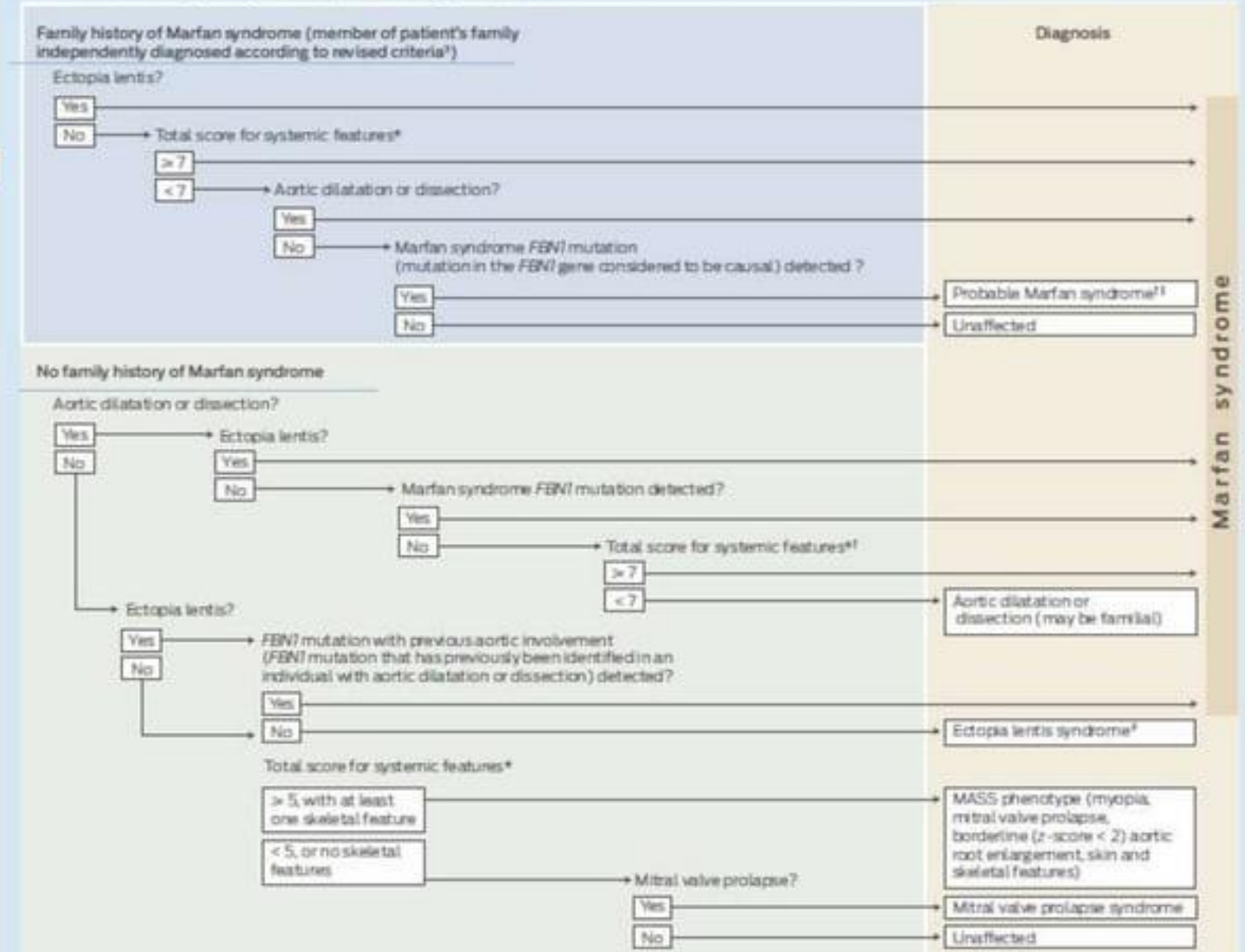
- History and physical examination (including slit-lamp ophthalmic examination with pupil dilation) in conjunction with imaging of the aortic root and the ascending, descending, and abdominal aorta (echo, CT, MRI) are usually sufficient for diagnosis.
- **Identification of risk factors**
  - Family history of Marfan's syndrome, or of aortic dissection or aneurysm.
  - There is also a weak association with high parental age.
- **Other historical considerations**
  - Family history of myopia, astigmatism, strabismus, amblyopia, premature cataract or other lens abnormalities, glaucoma, retinal detachment, dental extraction or braces for dental crowding, hernias, or spontaneous

- **Physical examination**
  - Tall stature, wide arm span, high level of pubic bone, high arched palate, arachnodactyly, positive wrist and thumb sign, pectus excavatum, pectus carinatum, scoliosis, striae, flat feet, thick spectacles for myopia, hernias, aortic or mitral valve murmur may be present.
  - Spontaneous pneumothorax or emphysematous bullae may present as dyspnoea.
  - There may be signs of heart failure due to valve disease or cardiomyopathy.
  - Complete ophthalmic examination, including fundus examination with pupil dilation - signs of lens subluxation or dislocation, cataract, glaucoma, or retinal detachment.
  - May present with acute aortic dissection or rupture.

- **Initial investigations**
  - Echocardiography, thorax CT, and thorax MRI are used initially for aortic root imaging.
  - Abdominal ultrasound, CT, and MRI are used for visualisation of the descending aorta.
  - CXR is performed to exclude the presence of a pneumothorax, and may reveal emphysematous bullae.

- **Subsequent investigations**
  - Blood screening for mutations in the fibrillin-1 (FBN1) gene confirms the diagnosis if in doubt. Once detected, the mutation can be used to screen other relatives, and used for antenatal diagnosis and pre-implantation genetic diagnosis. This test is more specific than MRI for dural ectasia, which can also be found in Ehlers-Danlos syndrome.
  - Lower spine CT scan or MRI can be performed to exclude dural ectasia.
  - Plasma homocysteine levels help in unclear cases to differentiate homocystinuria.
  - Skin biopsy is indicated only if Ehlers-Danlos syndrome is suspected.

1 Decision tree for diagnosing Marfan syndrome using revised criteria[3]



Differential diagnosis of Marfan syndrome

Differential diagnosis	Gene	Features similar to Marfan syndrome	Discriminating features
Loeys-Dietz syndrome (LDS)	TGFBR1/2	Aortic aneurysm/dissection	Bifid uvula/cleft palate, arterial tortuosity, hypertelorism, diffuse aortic and arterial aneurysms, craniosynostosis, clubfoot, cervical spine instability, thin and velvety skin, easy bruising
Shprintzen-Goldberg syndrome (SGS)	FBN1 and other	Pectus abnormalities, scoliosis, arachnodactyly	Craniosynostosis, mental retardation
MASS phenotype*	FBN1* and other	Mitral valve prolapse, mild aortic dilatation, striae atrophica, and at least one skeletal feature; systemic score ≥5	Aortic root size Z<2; no ectopia lentis
Mitral valve prolapse syndrome	Several candidate gene loci	Mitral valve prolapse, pectus excavatum, scoliosis, mild arachnodactyly	Lack of aortic enlargement, lack of ectopia lentis, systemic score <5
Congenital contractural arachnodactyly (CCA)	FBN2	Marfanoid habitus, arachnodactyly, kyphosis/scoliosis, mild enlargement of the sinuses of Valsalva	Crumpled ears (folded upper helix), contractures of major joints (knees and ankles) at birth, flexion contractures of the proximal interphalangeal joints (camptodactyly), absence of aortic dissection or rupture

Ectopia lentis syndrome (ELS)	FBN1, LTBP2, ADAMTSL4	Ectopia lentis, may have mild skeletal findings	Lack of aortic root dilatation
Familial thoracic aortic aneurysm and dissection syndrome (FTAAD/FTAA)	TGFBR1/2, ACTA2	Aortic dilatation and dissection	Livedo reticularis, iris flocculi, lack of Marfanoid skeletal features
Homocystinuria	CBS	Marfanoid habitus, ectopia lentis	Thrombosis, mental retardation
Arterial tortuosity syndrome (ATS)	SLC2A10	Aortic aneurysm	Generalized arterial tortuosity, arterial stenosis, facial dysmorphism
Ehlers-Danlos syndrome (vascular type)	COL3A1	Aortic aneurysm/dissection occurs in some	Middle sized artery aneurysm, translucent skin, dystrophic scars, intestinal or uterine rupture
Ehlers-Danlos syndrome (cardiac valvular subtype)	COL1A2	Mitral valve prolapse, joint hypermobility	Severe aortic and/or mitral valvular regurgitation, atrophic scars, skin hyperelasticity
Ehlers-Danlos syndrome (kyphoscoliotic type)	PLOD1	Aortic dilatation/dissection, kyphoscoliosis, joint laxity	Middle sized artery aneurysm/rupture
Stickler syndrome (hereditary arthroophthalmopathy)	COL2A1, COL11A1	Marfinoid habitus, mitral valve prolapse, retrognathia	Vitreal degeneration, retinal detachment, myopia, open angle glaucoma, early cataracts, cleft palate, hearing loss, epiphysial changes

Klinefelter's syndrome	47,XXY (and other X>1 genotypes in men)	Marfanoid habitus	Small testes and genitalia, cognitive impairment
Congenital bicuspid aortic valve disease with associated aortopathy	NOTCH1, KCNJ2, and putative loci on chromosomes 18q, 5q and 13q	Ascending aortic aneurysm, some have pectus deformity, scoliosis	Bicuspid aortic valve (may occur together with or separately from aortic aneurysm in various family members); lack of ocular and other systemic findings of Marfan syndrome; aortic dilatation is commonly maximal or exclusively above the sinotubular junction
Aortic coarctation with associated ascending aortic enlargement	NOTCH1, ERBB4, largely unknown	Aortic dilatation	Coarctation of the aorta

Summary and Recommendations

- The diagnosis of Marfan syndrome (MFS) in familial and sporadic cases are based upon the presence of characteristic manifestations, particularly aortic root dilatation/dissection and ectopia lentis, as well as other systemic features
- MFS is caused by a variety of mutations in the FBN1 gene. FBN1 mutations have been identified in over 90 percent of patients with MFS.
- Revised Ghent criteria is used for diagnosing Marfan syndrome.
- The differential diagnosis for MFS includes a variety of conditions with phenotypic features that partially overlap the Marfan phenotype, including disorders associated with FBN1/2 or TGFBR1/2 mutations, as well as a variety of other genetic disorders.

- First degree relatives of patients with a gene mutation associated with aortic aneurysms and/or dissection (eg, FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) should undergo counseling and genetic testing. Those found to have the genetic mutation should then undergo aortic imaging.
- For patients with aortic aneurysm and/or dissection without a known mutation, aortic imaging is recommended for first degree relatives to identify those with asymptomatic disease. If one or more first degree relatives are found to have thoracic aortic dilatation, aneurysm, or dissection, then imaging of second degree relatives is reasonable.

AHA/ACC/STS 2010 recommendations

- Echocardiography is recommended at initial diagnosis and at six months to assess the aortic root and ascending aorta in patients with MFS.
- Monitoring should be performed at least annually in patients with Ao root diameter more than 4.0 cm, and biannually in patients at higher risk (Ao root diameter more than 4.5 cm; Ao root enlargement more than 0.5 cm per year ; family history of Ao dissection).

AHA/ACC/STS 2010 recommendations

THANK YOU